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Low male partner attendance after syphilis screening in pregnant women leads to worse birth outcomes: the Syphilis Treatment of Partners (STOP) randomised control trial

Rosalind Parkes-Ratanshi[A,B,F], *Joshua Mbazira Kimeze*[A], *Edith Nakku-Joloba*[C], *Matthew M. Hamill*[D], *Mariam Namawejje*[A], *Agnes Kiragga*[A], *Josaphat Kayogoza Byamugisha*[E], *Anne Rompalo*[D], *Charlotte Gaydos*[D] *and Yukari C. Manabe*[D]

[A]Infectious Diseases Institute, Makerere University College of Health Sciences, PO Box 22418, Kampala, Uganda.
[B]Institute of Public Health, University of Cambridge, Forvie Site, Cambridge CB2 0SR, UK.
[C]School of Public Health, Makerere University College of Health Sciences, PO Box 7072, Kampala, Uganda.
[D]Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, 1830 E. Monument Street, Room 8031, Baltimore, MD 21287, USA.
[E]School of Medicine, Makerere University College of Health Sciences, PO Box 7072, Kampala, Uganda.
[F]Corresponding author. Email: rp549@medschl.cam.ac.uk

Abstract. ***Background*:** Maternal syphilis causes poor birth outcomes, including congenital syphilis. Testing and treatment of partners prevents reinfection, but strategies to improve partner attendance are failing. The aim of this study was to determine the effectiveness of three partner notification strategies. ***Methods*:** Pregnant women with a positive point-of-care treponemal test at three antenatal clinics (ANCs) in Kampala, Uganda, were randomised 1 : 1 : 1 to receive either notification slips (NS; standard of care), NS and a text messages (SMS) or NS and telephone calls. The primary outcome was the proportion of partners who attended the ANC and were treated for syphilis. ***Results*:** Between 2015 and 2016, 17 130 pregnant women were screened; 601 (3.5%) had a positive treponemal result, and 442 were enrolled in the study. Only 81 of 442 partners (18.3%; 23/152 (15.1%), 31/144 (21.5%) and 27/146 (18.5%) in the NS only, NS + SMS and NS + telephone call groups respectively) attended an ANC for follow-up; there were no significant differences between the groups. Twelve per cent of women attended the ANC with their male partner, and this proportion increased over time. Partner non-treatment was independently associated with adverse birth outcomes (odds ratio 2.75; 95% confidence interval 2.36–3.21; $P < 0.001$). ***Conclusions*:** Only 18.3% of partners of pregnant women who tested positive for syphilis received treatment. Female partners of non-attendant men had worse birth outcomes. Encouraging men to accompany women to the ANC and testing both may address the urgent need to treat partners of pregnant women in sub-Saharan Africa to reduce poor fetal outcomes.

Additional keywords: maternal syphilis, mobile phones, mother to child transmission, partner notification.

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Introduction

There are nearly 1 million cases of maternal syphilis globally annually,[1] causing adverse outcomes (low birthweight, stillbirth, preterm delivery and congenital syphilis) in up to 50% of untreated pregnancies.[2,3] Screening and treatment with single-dose benzathine penicillin for pregnant women is effective, inexpensive and demonstrated to be cost-effective.[4,5] In sub-Saharan Africa (SSA), it is estimated that universal antenatal screening could reduce the annual number of stillbirths, neonatal deaths and cases of congenital syphilis by up to 64 000, 25 000 and 32 000 respectively. Newer syphilis and combined HIV–syphilis point-of-care tests (POCT) help increase syphilis testing in pregnancy across the region.[6] Unless infected male partners of pregnant mothers are treated, reinfection later in the index pregnancy or subsequent pregnancies may occur. In Uganda, national health surveys show that 1.8% of adults aged 15–49 years have syphilis, and in 1% of couples both partners are infected.[7] Antenatal clinic (ANC) estimates are slightly higher, at 2.1–3.0%; neonatal mortality is 2.5%, with syphilis an important driver of adverse maternofetal outcomes.[8]

Partner notification (PN) has been used since the 19th century for sexually transmissible infection (STI) control[9] and aims to 'close the loop' of infection by ensuring all potentially infected partners of the index case are identified and treated. Different PN options are shown in Table 1. PN approaches have been studied extensively in resource-rich settings,[10,11] but there is little documentation of PN in Africa, especially for syphilis. A 2013 Cochrane review of PN randomised control trials (RCTs)[12] examined 24 studies, four of which were conducted in Africa. Only one of the 24 studies in that review, completed more than 20 years ago in the US,[13] examined PN strategies in syphilis. PN in resource-limited settings (RLS), such as SSA, is primarily accomplished through index patient notification because provider-oriented PN is costly;[14,15] this approach is encouraged by the World Health Organization (WHO).[16] The willingness of index patients to notify their partners has been shown to be high in SSA (58% in Uganda,[17] 50% in Rwanda[18] and 93% in Zimbabwe[15]). Furthermore, studies revealed that client counselling in Zambia[19] and Zimbabwe[15] increased PN for STIs. In Uganda, lower rates (25–34%) of partners attending for treatment have been observed,[17,20] including an attendance rate of 34.5% observed by our team at the Infectious Diseases Institute (IDI), Kampala for syphilis PN.[21] A 2010 review of PN strategies in RLS recommended index patient PN with counselling, but recognised the difficulty of implementation in such settings, with limited counsellors and lack of privacy.[14] A post-appointment follow-up interaction with index cases (in person or by telephone) has been shown to increase uptake of PN in gonorrhoea[22] and is a standard practice in HIV PN in SSA (including Uganda).[23]

Alam *et al.*[14] also proposed studies using mobile phone technology to support PN, which is attractive given the high levels of access to mobile phones in SSA. Forty-eight per cent of Ugandans have a mobile phone subscription.[24] However, mHealth studies in STIs are primarily pilot studies and efficacy data are lacking.[11,25] In order for PN through short messaging services (SMS), or text messages, to be viable ethically, confidentiality issues must be overcome.[26,27] SMS to index patients is ethically uncomplicated and may be an inexpensive way to encourage index patients to inform their partners in RLS, as has proven beneficial in high-income countries.[28]

We designed the Syphilis Treatment of Partners (STOP) trial to provide a low-cost, partially automated addition to improve on existing index case PN strategies of the Uganda Ministry of Health (paper notification slips). The approach was based on experience gained in PN at IDI with targeted counselling and standard of care (SOC; 58% informed their partner),[21] as well as from other African studies on index case PN.[15,29] The opportunity presented by increased mobile phone penetration could allow for inexpensive follow-up calls and automated SMS with a view to increasing partner attendance without large time and financial burdens. However, we wanted to avoid contacting partners directly due to confidentiality issues, so we added an additional post-test contact to the index case to increase PN. We anticipated that many of the barriers and facilitators in previously published STI and HIV studies would be similar for syphilis. We included both telephone and SMS because we speculated that deferential attitudes to healthcare providers (HCPs) may make HCP-initiated telephone calls more effective than SMS, but SMS are cheaper and therefore worth exploring. The aim of the study was to compare the proportion of partners who reported to the clinic for syphilis testing (and treatment) when syphilis-positive pregnant women were given only PN slips (SOC), compared with SOC plus SMS reminders or SOC plus telephone call reminders.

Methods

Participant recruitment

Between January 2015 and February 2016 pregnant women were identified in ANCs at Mulago Hospital and Kasangati Health Centre IV, both of which are Ministry of Health-run centres with busy ANCs, and the IDI Adult Infectious Disease Clinic, a private, not-for-profit clinic with an attached ANC in Kampala, Uganda. Potential participants were identified and approached by study staff. Screening was undertaken for syphilis using point-of-care (POC) lateral flow tests (SD Bioline; Standard Diagnostics, Gyeonggi-do, Republic of Korea). HIV status was established by self-report and, if unknown, women were offered testing using the rapid sequential algorithm. Those found to be positive were referred to HIV services if not previously in care. Women with a positive pregnancy test and treponemal antibody rapid POC test (POCT) were eligible for inclusion in the study. Other inclusion criteria were age >18 years or age 14–17 years and being a mature and emancipated minor (as defined by Ugandan National Science and Technology guidelines; https://www.uncst.go.ug/download/national-guidelines-for-research-involving-humans/, accessed 21 January 2020), having a known sexual partner, having access to a mobile phone and being willing and able to use and receive SMS or telephone calls. Exclusion criteria were illiteracy, inability to use a mobile

Table 1. Types of partner notification (PN)
EPT, expedited partner therapy; HCW, healthcare worker

Type of PN	Contacting index case	Follow-up
Provider-oriented methods	HCW or other third party	
Patient-oriented methods	Index patients	
Mixed methods	Index patients	HCW if index patient fails to notify
EPT	Index case provided with antibiotics to give to partner	Possible HCW follow-up

phone and confirmed neurosyphilis. Potential participants were offered information by study nurses and counsellors and examined to exclude neurosyphilis. Women were treated with 2.4 MU, i.m., benzathine penicillin G (BPG; in case of allergy, women were treated with azithromycin 2 g, p.o.). Participants provided informed written consent for randomisation and for temporary specimen (blood) storage. Serum was batched for rapid plasma reagin (RPR) testing with titre confirmation at the Walter Reed Research Laboratory in Kampala.

Women who attended with their partners were offered testing for HIV and syphilis, but were not included in the study because male partners were notified and treated for syphilis on the same day if their partner had a positive test.

Randomisation

Participants were randomised by a computer-generated block randomisation algorithm of different sized blocks in a ratio of 1 : 1 : 1 by an independent member of the IDI statistics team. The randomisation schedule was provided to the site in a box of sequentially numbered, opaque, sealed envelopes to the enrolling study nurses. The sequential randomisation codes were recorded on the study entry case report form to ensure randomisation adherence. All participants were given a written PN slip.

Intervention

The three study arms consisted of SOC (written PN slip), SOC plus SMS reminders and SOC plus telephone call reminders.

Standard of care

The PN slip was given to the pregnant female participant on the day she received her syphilis test results. The woman was asked to give the slip to her sexual partner(s) and encourage them to attend the STI clinic for syphilis management. The PN slip contained only a code number and no identifiable features.

SMS reminders and notification slip for partner screening

In this group, in addition to SOC, participants received weekly SMS reminders to encourage their partners to attend the STI clinic for syphilis testing for up to 8 weeks after the woman's initial positive syphilis test. The participant ID code number was written on the notification slip, which partners were asked to bring to the clinic, and in the SMS reminders. The script for the SMS is given in Table S1, available as Supplementary Material to this paper.

Telephone call reminders and notification slip for partner screening

In this group, in addition to SOC, participants received a weekly telephone call for up to 8 weeks after initial syphilis diagnosis from a nurse to remind them to encourage their partners to attend the STI clinic for syphilis testing (see Table S1 for the telephone call script). The participant ID code number was written on the notification slip, which partners were asked to return to the clinic, and was also given to the participant by nurse during the telephone calls.

Follow-up

All participants were encouraged to attend the ANC every 4 weeks until delivery. Notification slips were duplicated, with one copy to the pregnant woman and the other held in the clinic. On partner return, the slips were matched and used for linkage. The one postpartum study visit was conducted within 3 months of the end of pregnancy to assess clinical status, signs and symptoms, antibiotic side effects and adverse pregnancy outcomes as reported by the mothers, as well as to take a sample for serum storage. When possible, the mothers' knowledge of partner treatment (place, type of treatment etc.) were captured. When the mother failed to attend, the study team performed a follow-up telephone call or home visit to the woman or recorded next of kin. If the mother had experienced a stillbirth or neonatal death in this pregnancy, she was offered counselling. If a baby had signs or symptoms of congenital syphilis, a referral was made to the National Referral Hospital for medical evaluation.

When the male partner attended the STI clinic as a result of a notification, informed consent to collect study-related data was obtained. Men underwent testing for syphilis using a rapid treponemal antibody test followed by RPR confirmation. All men attending were given syphilis treatment (as above) on the same visit regardless of their syphilis results as per Ministry of Health guidelines. Any partner attendance reported through verbal confirmation by the mother or physical attendance by the partner for treatment between the time of registration and the maternal postnatal visit was included in the analysis.

Women received a small travel reimbursement (US$8), but this was not given to male partners to avoid financial incentive for attendance.

Sample size

The sample size was calculated using data from the IDI clinic located within urban Kampala, where 220 pregnant women are seen at the ANC per month, 5.1% of whom test positive for syphilis,[21] and the Mulago Hospital ANC, where, on average, 2000 pregnant women are seen monthly, with 2.4% testing positive for syphilis.[8] Based on a previous study at the IDI with targeted counselling and SOC, we estimated that 50% of women would notify their partners and that 60% of those notified would attend the clinic in the SOC arm (overall 30% of male partners).[21] We hypothesised that if counselling and the PN slip alone resulted in 30% partner attendance, then additional interventions with reminders (SMS, telephone calls) would have a positive effect, resulting in increased partner attendance (for gonorrhoea, 1 interview = 13% partner attendance vs >1 interview = 60% partner attendance[22]). In order to show a 50% increase in the proportion of partners of women attending for testing and treatment in the intervention arms (45% of male partners overall), we estimated a sample size of 292 women per arm with a total of 876 participants. To account for multiple comparisons of the effect of each of the interventions with the SOC arm, a Type 1 error (α) of 1.67% was set.

Data analysis

The primary outcome was the proportion of partners who presented at the clinic and received syphilis testing or treatment. Pearson's Chi-squared statistic was used to test for

significant differences among the three arms. In addition, the proportion of men who tested positive for syphilis, the proportion who received syphilis treatment from the ANC and those reported by their spouse or partner to have received treatment elsewhere were compared among arms using the Chi-squared statistic. For some analyses we combined birth outcomes into positive outcomes (live mother and baby) and negative, rarer, outcomes (miscarriage, stillbirth, preterm labour, birth defects, neonatal death as reported by the enrolled mothers). A multivariable logistic regression model with robust standard errors was used to establish factors associated with negative pregnancy outcomes. In this model, the notification arm was the primary exposure variable, whereas age, marital status, employment and treatment of partner for syphilis were considered potential confounders. All analyses were performed using STATA 15.1 (StataCorp, College Station, TX, USA).

Ethics approvals

Ethics approval was obtained from the Ugandan Joint Clinical Research Centre Institutional Review Board (IRB), the Uganda National Council for Science and Technology (HS1681) and the Johns Hopkins IRB (NA_00012998/CR00015330). The trial was registered at Clinicaltrials.gov (NCT02262390). The study adhered to Consolidated Standards of Reporting Trials (CONSORT) guidelines (http://www.consort-statement.org/Media/Default/Downloads/CONSORT%202010%20Statement/CONSORT%202010%20Statement%20(BMJ).pdf, accessed 21 January 2020) in methods and reporting.

Results

Syphilis screening

In all, 17 130 participants were interviewed between January 2015 and February 2016 (Fig. 1) and follow-up was completed by April 2017. The median age of the pregnant women screened was 25 years (interquartile range (IQR) 22–28 years), 15 094 (88.1%) were married and median parity was 2 (IQR 1–4); 601 (3.5%) tested positive for treponemal antibody. Of 16 805 women whose HIV status was known, 808 (4.8%) were HIV positive. Syphilis prevalence was higher among HIV-positive than -negative women (67/808 (8.3%) vs 535/16 322 (3.3%) respectively). One-fifth (20.2%) of women reported a negative outcome in a previous pregnancy (20.1% of those who were syphilis negative vs 23.3% who were syphilis positive; $P < 0.001$; Table S2). Of 601 women with positive syphilis tests, 71 (11.8%) were not enrolled in the study because they did not have a telephone, 55 (9.2%) were not enrolled because they attended the clinic with their partner and 33 (5.5%) were not enrolled for other reasons (Fig. 1). The number of women attending with their partner for the first antenatal visit increased over time (Fig. S1). Of 442 pregnant women enrolled in the study, all were rapid test positive, 404 (91.4%) were RPR positive, 36 (8.1%) were RPR negative and two RPR results (0.45%) were missing. Of the positive RPRs at enrolment, 156/404 (38.6%) were $\geq$1 : 8. All women who were treponemal antibody positive received BPG.

Study enrolment

Overall, 442 pregnant women were enrolled in the study: 152 (34.4%) in SOC arm, 144 (32.6%) in the SOC + SMS arm and 146 (33.0%) in the SOC + telephone call arm. Most participants (362/442; 81.9%) were enrolled from the Mulago site, and 185 (41.9%) and 220 (49.8%) had primary- or secondary-level education respectively. Most women were in their second trimester (251/442; 56.8%), and 28 (6.3%) were HIV positive (Table 2).

Postenrolment partner attendance

Postenrolment partner attendance at study sites was very low (18.2%; 81/442). In the SOC, SOC + SMS and SOC + telephone

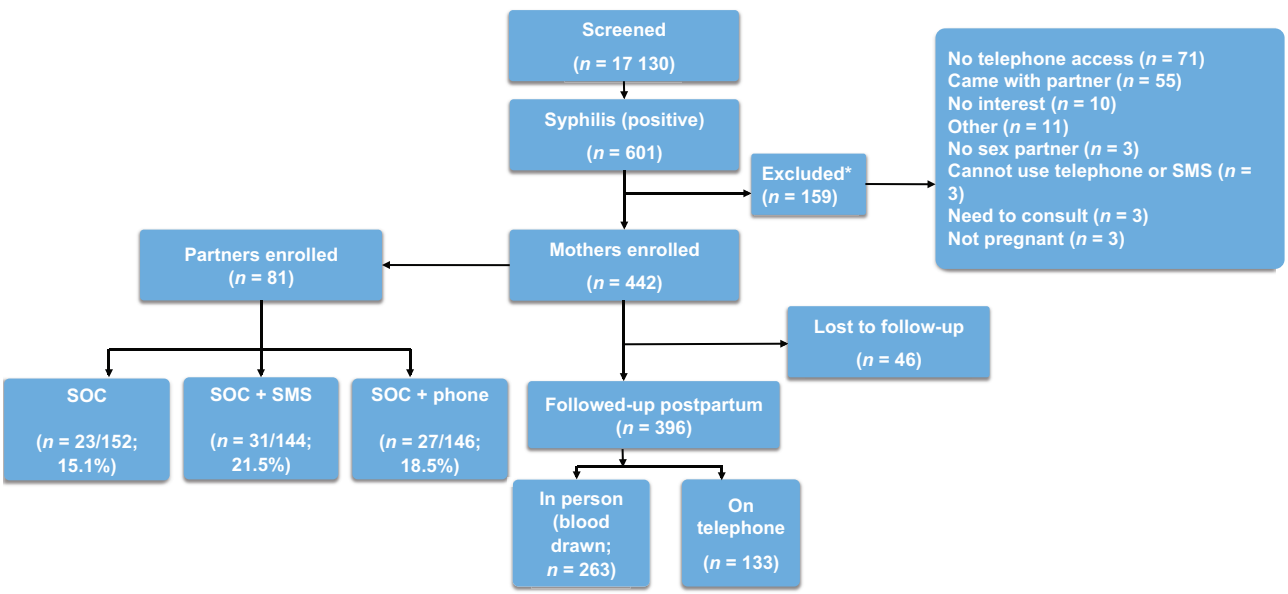

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. *Ten women had more than one reason for exclusion. SMS, short messaging service (text message); SOC, standard of care (consisting of partner notification slips handed to women attending the clinic).

Table 2. Baseline demographic and clinical characteristics of enrolled mothers

Unless indicated otherwise, data are given as *n* (%). IDI AIDC, Infectious Diseases Institute – Adult Infectious Diseases Clinic; IQR, interquartile range; SMS, short messaging service (text message); SOC, standard of care (consisting of partner notification slips handed to women attending the clinic)

Variable	SOC (*n* = 152)	Slip + SMS reminder (*n* = 144)	Slip + nurse telephone call (*n* = 146)	Overall population (*n* = 442)
Site				
IDI AIDC	4 (2.6)	4 (2.8)	2 (1.4)	10 (2.3)
Mulago	129 (84.9)	118 (81.9)	115 (78.8)	362 (81.9)
Kasangati	19 (12.5)	22 (15.3)	29 (19.9)	70 (15.8)
Median [IQR] age (years)	26 [24–29]	27 [24–30]	26 [23–29]	26 [23–30]
Marital status				
Monogamous marriage	111 (73.0)	96 (66.7)	119 (81.5)	326 (73.8)
Polygamous marriage	35 (23.0)	39 (27.1)	23 (15.7)	97 (22.0)
Separated or divorced	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)
Single, regular partner	5 (3.3)	7 (4.9)	4 (2.7)	16 (3.6)
Single, irregular partner	1 (0.7)	1 (0.7)	0 (0.0)	2 (0.5)
Education level				
None	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)
Primary	54 (35.5)	67 (46.5)	64 (43.8)	185 (41.9)
Secondary	84 (55.3)	68 (47.2)	68(46.6)	220 (49.8)
Tertiary	13 (8.6)	7 (4.9)	14 (9.6)	34 (7.7)
Missing	1 (0.7)	1 (0.7)	0 (0.0)	2 (0.5)
Currently employed				
Yes	70 (46.0)	88 (61.1)	77 (52.7)	235 (53.2)
HIV status				
Negative	138 (90.8)	135 (93.7)	136 (93.2)	409 (92.5)
Positive	11 (7.2)	7 (4.9)	10 (6.8)	28 (6.3)
Missing	3 (2.0)	2 (1.4)	0 (0.0)	5 (1.1)
Gravida				
1	14 (9.2)	12 (8.3)	18 (12.3)	44 (9.9)
2	36 (23.7)	30 (20.8)	33 (22.6)	99 (22.4)
≥3	102 (67.1)	102 (70.8)	95 (65.1)	299 (67.7)
Pregnancy planned				
Yes	120 (79.0)	115 (80.4)	129 (88.4)	364 (82.5)
Pregnancy trimester				
First	9 (5.9)	10 (6.9)	7 (4.8)	26 (5.9)
Second	83 (54.6)	76 (52.8)	92 (63.0)	251 (56.8)
Third	60 (39.5)	58 (40.3)	47 (22.2)	165(37.3)

call arms, 23 of 152 (15.1%), 31 of 144 (21.5%) and 27 of 146 (18.5%) partners returned to the study site respectively. There were no significant differences between study-documented postenrolment partner attendance by method of PN (Person's Chi-squared, $P = 0.363$; Table 3). An interim futility analysis suggested that there would be no significant difference seen in the arms of the study with the original sample, which led to cessation of enrolment before the original sample size of the study was reached.

The characteristics of the male partners who attended at study sites are given in Table 4. The mother was not aware of partner clinic attendance for 12 of 81 men (14.8%) who reported for treatment at study sites. Of the 81 men who attended clinic study sites, 21 (25.9%) tested positive for syphilis; there was no difference in the rates of syphilis positivity in male partners among the study arms ($P = 0.267$). An additional 17 mothers reported that their partners had attended a non-study clinic or health facility for syphilis treatment, which increased the total rate to 98 of 442 male partners (22.2%) accessing treatment. When these men were included in the analysis, 27 of 98 (22.2%) were in the SOC arm, 35 (35.7%) were in the SMS arm and 36 (36.7%) were in the telephone call arm ($P = 0.151$).

Mother and baby outcomes

In all, 396 enrolled women (89.6%) were followed-up by telephone call ($n = 133$; 33.6%) or an in-person visit ($n = 263$; 66.4%): 136 (34.3%), 131(33.1%) and 129 (32.6%) from the SOC, SOC + SMS and SOC + telephone call arms respectively. Of these 396 women, only 22 did not give the notification slip to their partner (10/136 (7.4%), 4/131 (3.1%) and 8/129 (6.2%) in the SOC, SOC + SMS and SOC + telephone call arms respectively). Among the women who were followed-up, 372 (93.9%) had a healthy delivery at term, two (0.5%) had preterm births, 13 (3.3%) had spontaneous or induced abortions and nine (2.3%) had stillbirths. In all, there were 24 (6.1%) negative pregnancy outcomes (preterm births, abortion,

Table 3. Partner attendance according to study notification arm

The three study arms consisted of standard of care (SOC; a written partner notification slip (NS) was given to the woman), SOC plus short messaging service (SMS) reminders and SOC plus telephone call reminders. Unless indicated otherwise, data are given as *n*/*N* (%), where *n* is the number of partners attending and *N* is the number of women in each group. IDI AIDC, Infectious Diseases Institute – Adult Infectious Diseases Clinic; IQR, interquartile range

	SOC (*n* = 152)	SOC + SMS reminder (*n* = 144)	SOC + nurse telephone call (*n* = 146)	Overall population (*n* = 442)
Partner attendance	23/152 (15.1)	31/144 (21.5)	27/146 (18.5)	81/442 (18.3)
IDI AIDC (*n* = 10)	0/4 (0.0)	1/4 (25.0)	1/2 (50.0)	2/10 (20.0)
Mulago (*n* = 362)	16/129 (12.4)	25/118 (21.2)	22 /115 (19.1)	63/362 (17.4)
Kasangati (*n* = 70)	7/19 (36.8)	5/22 (22.7)	4/29 (13.8)	16/70 (22.8)
Median (IQR) interval from delivery of NS to woman and partner clinic visit (days)	20 [5–35]	20 [6–42]	22 [7–30]	21 [6–35]

Table 4. Demographic characteristics of male partners enrolled in the study

Unless indicated otherwise, data are given as *n* (%). IDI AIDC, Infectious Diseases Institute – Adult Infectious Diseases Clinic; IQR, interquartile range

Variable	Male partner diagnosed with syphilis		Overall male partner population (*n* = 78[A])
	No (*n* = 59)	Yes (*n* = 19)	
Site			
IDI AIDC	2 (3.9)	0 (0.0)	2 (2.6)
Mulago	45 (76.3)	15 (79.0)	60 (76.9)
Kasangati	12 (20.3)	4 (21.0)	16 (20.5)
Median [IQR] age (years)	30 [26–39]	31 [28–38]	26 [23–30]
Marital status			
Monogamous marriage	47 (79.7)	14 (73.7)	61 (78.2)
Polygamous marriage	12 (20.3)	5 (26.3)	17 (21.8)
Education level			
None	1 (1.7)	1 (5.2)	2 (2.6)
Primary level	21 (35.6)	6 (31.6)	27 (34.6)
Secondary level	27 (45.7)	8 (42.1)	35 (44.8)
Tertiary	10 (17.0)	3 (15.8)	13 (16.7)
Professional qualifications	0 (0.0)	1 (5.2)	1 (1.3)
Currently employed			
Yes	57 (96.6)	19 (100.0)	76 (97.4)
History of HIV testing			
Negative	52 (88.1)	18 (94.7)	70 (89.7)
Positive	4 (6.8)	1 (5.3)	5 (6.5)
Never tested	3 (5.1)	0 (0.0)	3 (3.8)
Ever diagnosed with syphilis			
Yes	6 (10.2)	10 (52.6)	16 (20.5)

[A]Three partners who returned to the clinic had missing syphilis test results.

Table 5. Multiple logistic regression model showing factors associated with negative pregnancy outcomes among women who returned for follow-up

The model was adjusted for reproductive history and HIV status. Correlation between sites was accounted for using robust standard errors. Negative outcomes include preterm births, abortion, stillbirth and miscarriages. aOR, adjusted odds ratio; CI, confidence interval; SMS, short messaging service (text message); SOC, standard of care (consisting of partner notification slips handed to women attending the clinic)

Variable	aOR (95% CI)	*P*-value
Each 5-year increase in age	1.55 (1.33–1.79)	<0.001
Marital status		
Monogamous marriage	1	
Polygamous marriage	2.59 (1.12–5.99)	0.025
Single or divorced	2.94 (0.04–226.40)	0.625
Employment status		
Currently employed	1	
Unemployed	1.19 (1.02–1.40)	0.028
Partner treated for syphilis		
Yes	1	
No	2.75 (2.36–3.21)	<0.001
Notification arm		
SOC	1	
SOC + SMS	1.80 (0.96–3.38)	0.068
SOC + telephone call	0.99 (0.50–2.01)	0.996

stillbirth, and miscarriages): 7/136 (5.2%), 11/131 (8.4%) and 6/129 (4.6%) in the SOC, SOC + SMS and SOC + telephone call arms respectively ($P = 0.386$). Among the 86 women whose partners received treatment for syphilis, two (2.3%) experienced negative pregnancy outcomes, compared with 22 of the 310 women (7.1%) whose partners were not treated ($P = 0.127$). In the multivariable logistic regression model (Table 5), the risk of having a negative pregnancy outcome increased significantly under the following conditions: with every 5-year age increase, among women in polygamous versus monogamous marriages, in women whose partners were untreated for syphilis and for unemployed women. In a sensitivity analysis where all women who were lost to follow-up were considered to have negative pregnancy outcomes, the results were similar.

Discussion

This is the first reported RCT of PN approaches to antenatal syphilis in SSA and the first major trial of syphilis PN in 20 years. This study was large, screening over 17 000 pregnant women and recruiting over 400 female participants. Syphilis seropositivity rates were high at 3.5%. The study tested SOC index case notification against mobile phone-based

methods, which are cheap and widely available in SSA. Overall, this study in Ugandan ANCs achieved a post-enrolment partner attendance of 18.3%, with no significant differences seen between the methods used (notification slip, telephone call or SMS). A major finding of the study was that partner non-treatment was independently and significantly associated with adverse birth outcomes on multivariate analysis.

This study demonstrated much lower partner attendance than previously published work. In Kenya, a partner notification study in primary care showed 68% notified their partner and 58% reported their partner had attended for STI treatment.[29] In Uganda, reported partner attendance rates have been lower, at 25–34.5%.[17,20,21] This low attendance rate was a major limitation of the present study. A futility analysis was undertaken, which led to enrolment being capped at 422 of the 876 planned enrolments; resources were not available to markedly increase the sample size required to adequately power the primary outcome. There are several reasons for low attendance that highlight the limitations of the study, including mothers not informing the male partner, the male partner being informed but not attending, the male partner attending but not telling the mother and male partners who were more likely to receive treatment being screened out of the study. These reasons are explored below.

Previous published studies on PN for STIs in RLS revealed barriers including lack of knowledge of STIs, stigma, fear of domestic violence, fear of revealing extramatrimonial partners or an inability to contact casual partners.[14] Therefore, numerous cultural and systemic barriers exist at all stages of the pathway from the point where the woman is diagnosed with syphilis to the point where she informs her partner(s), clinic attendance and the partner(s) receiving appropriate testing and treatment. An additional limitation of the present study and a key lesson learned is that we perhaps did not go far enough to break down some of these barriers despite our previous work in this area.[21] Ideally, we should have undertaken syphilis-specific intervention development work with pregnant women, but our low-resource approach did not allow for dedicated counselling time. We had anticipated that a clinic-generated SMS shown to a partner or a witnessed telephone call may have facilitated discussions between partners. In a qualitative substudy we showed poor partner communication, stigma and fear of intimate partner violence as barriers to PN.[30]

Two recent studies have shown that those with an STI are supportive of index case PN. In South Africa, 91% of men in a high-risk group would prefer notification of an STI by slip from their partner, but only 62.7% felt that an SMS from a healthcare worker was acceptable.[31] In Uganda, index case PN was deemed highly acceptable by most groups, and HCPs voiced concerns about limited time, resources and training for provider-assisted approaches.[32] These findings suggest that index cases are prepared to inform their partners, but getting partners to attend is the issue. Another limitation of the present study is that we did not collect data on who had told their partner, just whether the partner had attended or not.

The qualitative substudy identified limited knowledge of syphilis as the main reason for a lack of partner attendance.[30] In order to strengthen our approach, a series of staged information messages about syphilis via text message or voice call, rather than just notification reminders, may have had more impact and is worthy of future study. Another issue highlighted by the qualitative work was the poor communication between partners. Notably, 15% of men attended for treatment without notifying their pregnant partner. This could also have contributed to an underestimate of the number of men attending for treatment.

The low partner attendance rate we saw may be due to the exclusion of women who attended the ANC with their partner; overall, we excluded 12% (74/601) of syphilis-positive women whose partners attended with them, because these partners were tested and treated for syphilis on the same day. The increase in male partner attendance over time demonstrates that the ongoing Ministry of Health strategy encouraging male partner attendance at ANCs had a positive effect during the course of this study. Therefore, we hypothesise that widespread availability of syphilis and HIV testing for mothers and their partners, along with patient educational interventions, could improve syphilis screening uptake. It is striking that there were relatively low rates of syphilis in the men who did attend for testing (25.9%), challenging the assumption that untreated male partners are the predominant driver of syphilis in pregnancy. We speculate that those men who did attend were more willing and/or better able to engage with the health system and systematically different from those who did not attend.

There is a possibility of unmeasured confounding by site selection; there are disparities in care across healthcare settings in Uganda generally, but inclusion of three different settings, all with low partner attendance rates, may indicate the problem is generalised across different settings. Other obstacles include refurbishment of Mulago Hospital and consequent relocation of the ANC, which created difficulties for mothers to attend follow-up appointments within the study limits. This resulted in missing post-treatment RPR data in many, making conclusions about longitudinal RPR results impossible. Previous work in Tanzania showed that women with high syphilis RPR titres (>1 : 8) indicating active syphilis had a stillbirth rate of 25% compared 1% in uninfected women (risk ratio [RR], 18.1; P<.001);[3] however, it is not possible to infer whether negative pregnancy outcomes were likely due to congenital syphilis in the present study.

Since this study was undertaken, Uganda has embraced assisted PN for HIV testing alongside WHO encouragement of this approach.[33] Index cases found to be HIV positive enter into an agreement with healthcare workers that they will notify their partners within a certain time period. If they have not done this by the time they are contacted again, the health worker will undertake contact PN if the index case agrees.[34] The HIV-positive women are supported by counselling to help communication with their partner, including strategies such as role play if necessary. With this regulatory change, the study team feels that assisted PN may be a preferable method for syphilis PN moving forward. However, in our qualitative work, mothers were concerned about intimate partner violence against mothers who disclose partner details or admit to having an STI, so this needs to be seriously considered if men are to be contacted directly by HCPs.[30] Regulatory frameworks covering non-HIV STIs would be

welcome to support healthcare workers in choosing the best method of PN, including assisted PN.

Conclusion

This study screened over 17 000 pregnant women and, by the end of the study, 12% had attended the clinic with their male partners but only 18% of men attended after receiving a partner notification. Treatment of male partners for syphilis is extremely important, as demonstrated by more negative birth outcomes in women with untreated partners. SMS and telephone calls remain potentially useful and underused tools in STI partner management in RLS, but have not yet been fully evaluated. Further studies to stop the cycle of reinfection of mothers and congenital syphilis are needed, and the role of men in the solution cannot be overlooked if progress is to be made.

Conflicts of interest

Rosalind Parkes-Ratanshi receives grant funding through the IDI from Janssen, the pharmaceutical company of Johnson and Johnson. The other authors have no conflicts of interest to disclose.

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References

1 Wijesooriya NS, Rochat RW, Kamb ML, Turlapati P, Temmerman M, Broutet N, *et al*. Global burden of maternal and congenital syphilis in 2008 and 2012: a health systems modelling study. *Lancet Glob Health* 2016; 4: e525–33. doi:10.1016/S2214-109X(16)30135-8

2 Gomez GBKM, Newman LM, Mark J, Broutet N, Hawkes SJ. Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis. *Bull World Health Organ* 2013; 91: 217–26. doi:10.2471/BLT.12.107623

3 Watson-Jones D, Changalucha J, Gumodoka B, Weiss H, Rusizoka M, Ndeki L, *et al*. Syphilis in pregnancy in Tanzania. I. Impact of maternal syphilis on outcome of pregnancy. *J Infect Dis* 2002; 186: 940–7. doi:10.1086/342952

4 Kuznik A, Lamorde M, Nyabigambo A, Manabe YC. Antenatal syphilis screening using point-of-care testing in sub-Saharan African countries: a cost-effectiveness analysis. *PLoS Med* 2013; 10: e1001545. doi:10.1371/journal.pmed.1001545

5 Watson-Jones D, Gumodoka B, Weiss H, Changalucha J, Todd J, Mugeye K, *et al*. Syphilis in pregnancy in Tanzania. II. The effectiveness of antenatal syphilis screening and single-dose benzathine penicillin treatment for the prevention of adverse pregnancy outcomes. *J Infect Dis* 2002; 186: 948–57. doi:10.1086/342951

6 Swartzendruber A, Steiner RJ, Adler MR, Kamb ML, Newman LM. Introduction of rapid syphilis testing in antenatal care: a systematic review of the impact on HIV and syphilis testing uptake and coverage. *Int J Gynaecol Obstet* 2015; 130: S15–21. doi:10.1016/j.ijgo.2015.04.008

7 Ministry of Health, The Republic of Uganda. Status report on the global fund grants in Uganda. 2011. Available online at: http://www.health.go.ug/MoH/docs/global_fund.pdf [verified 16 September 2019].

8 Ministry of Health Uganda, The Republic of Uganda. Uganda AIDS indicator survey (AIS) 2011. 2012. Available online at: http://health.go.ug/docs/UAIS_2011_REPORT.pdf [verified 28 September 2018].

9 Cowan FM, French R, Johnson AM. The role and effectiveness of partner notification in STD control: a review. *Genitourin Med* 1996; 72: 247–52. doi:10.1136/sti.72.4.247

10 Althaus CL, Turner KM, Mercer CH, Auguste P, Roberts TE, Bell G, *et al*. Effectiveness and cost-effectiveness of traditional and new partner notification technologies for curable sexually transmitted infections: observational study, systematic reviews and mathematical modelling. *Health Technol Assess* 2014; 18: 1–100. doi:10.3310/hta18020

11 Pellowski J, Mathews C, Kalichman MO, Dewing S, Lurie MN, Kalichman SC. Advancing partner notification through electronic communication technology: a review of acceptability and utilization research. *J Health Commun* 2016; 21: 629–37. doi:10.1080/10810730.2015.1128020

12 Ferreira A, Young T, Mathews C, Zunza M, Low N. Strategies for partner notification for sexually transmitted infections, including HIV. *Cochrane Database Syst Rev* 2013; 10: CD002843. doi:10.1002/14651858.CD002843.pub2

13 Peterman TA, Toomey KE, Dicker LW, Zaidi AA, Wroten JE, Carolina J. Partner notification for syphilis: a randomized, controlled trial of three approaches. *Sex Transm Dis* 1997; 24: 511–18. doi:10.1097/00007435-199710000-00003

14 Alam N, Chamot E, Vermund SH, Streatfield K, Kristensen S. Partner notification for sexually transmitted infections in developing countries: a systematic review. *BMC Public Health* 2010; 10: 19. doi:10.1186/1471-2458-10-19

15 Moyo W, Chirenje ZM, Mandel J, Schwarcz SK, Klausner J, Rutherford G, *et al*. Impact of a single session of counseling on partner referral for sexually transmitted disease treatment, Harare, Zimbabwe. *AIDS Behav* 2002; 6: 237–43. doi:10.1023/A:1019891808383

16 WHO/UNAIDS. Sexually transmitted diseases: policies and principles for prevention and care. 1999. Available online at: http://data.unaids.org/publications/irc-pub04/una97-6_en.pdf [verified 16 September 2019].

17 Kamali A, Quigley M, Nakiyingi J, Kinsman J, Kengeya-Kayondo J, Gopal R, *et al*. Syndromic management of sexually-transmitted infections and behaviour change interventions on transmission of HIV-1 in rural Uganda: a community randomised trial. *Lancet* 2003; 361: 645–52. doi:10.1016/S0140-6736(03)12598-6

18 Steen R, Soliman C, Bucyana S, Dallabetta G. Partner referral as a component of integrated sexually transmitted disease services in two Rwandan towns. *Genitourin Med* 1996; 72: 56–9. doi:10.1136/sti.72.1.56

19 Faxelid E, Tembo G, Ndulo J, Krantz I. Individual counseling of patients with sexually transmitted diseases. A way to improve partner notification in a Zambian setting? *Sex Transm Dis* 1996; 23: 289–92.

20 Nuwaha F, Faxelid E, Wabwire-Mangen F, Eriksson C, Hojer B. Psycho-social determinants for sexual partner referral in Uganda: quantitative results. *Soc Sci Med* 2001; 53: 1287–301. doi:10.1016/S0277-9536(00)00410-X

21 Manabe YC, Namale G, Nalintya E, Sempa J, Ratanshi RP, Pakker N, *et al*. Integration of antenatal syphilis screening in an urban HIV clinic: a feasibility study. *BMC Infect Dis* 2015; 15: 15. doi:10.1186/s12879-014-0739-1

22 Bell G, Ward H, Day S, Ghani AC, Goan U, Claydon E, *et al*. Partner notification for gonorrhoea: a comparative study with a provincial and a metropolitan UK clinic. *Sex Transm Infect* 1998; 74: 409–14. doi:10.1136/sti.74.6.409

23 Hammett TM, Kayongo M, Potts C, Brouhard K, Thompson C, Chintalova-Dallas R, Kravitz Del Solar A. Partner notification: a handbook for designing and implementing programs and services. 2016. Available online at: https://aidsfree.usaid.gov/sites/default/files/2018.6.19_pn-handbook.pdf [verified 16 September 2019].

24 International Telecommunication Union. Mobile-cellular subscriptions (per 100 people) 2000–2014 country data. 2015. Available online at: https://data.worldbank.org/indicator/IT.CEL.SETS.P2 [verified 16 September 2019].

25 Hochberg CH, Berringer K, Schneider JA. Next-generation methods for HIV partner services: a systematic review. *Sex Transm Dis* 2015; 42: 533–9. doi:10.1097/OLQ.0000000000000335

26 Mookherji S, Mehl G, Kaonga N, Mechael P. Unmet need: improving mHealth evaluation rigor to build the evidence base. *J Health Commun* 2015; 20: 1224–9. doi:10.1080/10810730.2015.1018624

27 Hermans SM, Elbireer S, Tibakabikoba H, Hoefman BJ, Manabe YC. Text messaging to decrease tuberculosis treatment attrition in TB–HIV coinfection in Uganda. *Patient Prefer Adherence* 2017; 11: 1479–87. doi:10.2147/PPA.S135540

28 Bilardi JE, Fairley CK, Hopkins CA, Hocking JS, Sze JK, Chen MY. Let them know: evaluation of an online partner notification service for chlamydia that offers E-mail and SMS messaging. *Sex Transm Dis* 2010; 37: 563–5. doi:10.1097/OLQ.0b013e3181d707f1

29 Njeru EK, Eldridge GD, Ngugi EN, Plummer FA, Moses S. STD partner notification and referral in primary level health centers in Nairobi, Kenya. *Sex Transm Dis* 1995; 22: 231–5. doi:10.1097/00007435-199507000-00006

30 Nakku-Joloba E, Kiguli J, Kayemba CN, Twimukye A, Mbazira JK, Parkes-Ratanshi R, *et al*. Perspectives on male partner notification and treatment for syphilis among antenatal women and their partners in Kampala and Wakiso districts, Uganda. *BMC Infect Dis* 2019; 19: 124. doi:10.1186/s12879-019-3695-y

31 Mokgatle MM, Madiba S. Intentions to use patient-initiated partner notification and acceptability of provider-initiated partner notification for sexually transmitted infections – a cross-sectional survey among minibus taxi drivers in Gauteng Province, South Africa. BioRXIV; 2018. Available online at: https://www.biorxiv.org/content/10.1101/502724v1 [verified 21 November 2019].

32 Quinn C, Nakyanjo N, Ddaaki W, Burke VM, Hutchinson N, Kagaayi J, *et al*. HIV partner notification values and preferences among sex workers, fishermen, and mainland community members in Rakai, Uganda: a qualitative study. *AIDS Behav* 2018; 22: 3407–16. doi:10.1007/s10461-018-2035-3

33 World Health Organization. Guidelines on HIV testing services HIV self-testing and partner notification. Supplement to consolidated guidelines on HIV testing services. 2016. Available online at: https://apps.who.int/iris/bitstream/handle/10665/251655/9789241549868-eng.pdf [verified 16 September 2019].

34 Ministry of Health Uganda. National HIV testing services policy and implementation guidelines Uganda. Kampala: Government of Uganda; 2016.